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REVIEW ARTICLE

Chronic constipation: no more idiopathic, but a true neuropathological entity

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ABSTRACT

Chronic constipation is still considered a functional or idiopathic disorder. However, in recent years there is evidence that its pathopysiological grounds may be actually due to a complex system of abnormalities of the enteric nervous system of these patients. In particular, as reported in this review, the enteric glial cells seem to be constantly involved in constipated patients, suggesting that (at least some forms of) constipation should be considered as true neuro-gliopathies.

Keywords: Constipation, Enteric glial cells, Enteric neurons, Enteric nervous system

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Introduction

In recent years, the improvement of technology and the increase in knowledge have shifted several strongly held paradigms. This is particularly true in gastroenterology, and specifically in the field of the so-called "functional" or "idiopathic" disease, where conditions thought for decades to be based mainly on alterations of visceral perception or aberrant psychosomatic mechanisms have, in fact, be reconducted to an organic basis (or, at the very least, have shown one or more demonstrable abnormalities).

This is particularly true, for instance, for irritable bowel syndrome (IBS), the prototype entity of functional gastrointestinal (GI) disorders, where low-grade inflammation of both mucosa and myenteric plexus has been repeatedly demonstrated (1, 2). Thus, researchers have also investigated other functional/idiopathic GI disorders, and found that some organic ground is present, such as abnormal neurotransmission and myenteric plexitis in esophageal achalasia (3-5) and mucosal immune activation and mild eosinophilia in functional dyspepsia (6, 7).

Here we show evidence, based on our own and other authors' work, that chronic constipation should no more be considered as a functional/idiopatic GI disorder, but instead as a true enteric neuropathic abnormality.

What is known about pathophysiology of chronic constipation?

Chronic constipation is a frequent disorder, characterized by reduction of bowel movements

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and/or defecatory difficulties (8) but probably represents a multifaceted entity that may be broadly classified in two main subgroups (i.e., slow transit constipation, STC, and obstructed defecation, OD) (9).

The pathophysiological grounds of constipation have been traditionally attributed to the dysfunction of anorectal (10-16) and/or colonic motility (17, 18), even though the basic mechanisms responsible for this dysfunction still remains quite obscure. However, there is some evidence that constipated patients may have qualitative and quantitative changes in the enteric nervous system (ENS) of the colon such as abnormal enteric neurochemistry (19-21), reduction of intraganglionic neurofilaments (22), myenteric plexus hypoganglionosis (23), and decreased colonic interstitial cells of Cajal (ICC) (24, 25), even though discrepancies have been reported in other studies (26, 27).

Recent neuropathological findings in chronic constipation

In these last years, thanks to the availability of full-thickness surgical specimens from patients with different subtypes of chronic constipation, we were able to investigate in a more comprehensive way some abnormalities of the ENS present in these subjects.

One of the subtypes of constipation more often labeled as intractable and refractory to any form of medical treatment is STC (28, 29), a form that sometimes requires a surgical approach (30). In a study on surgically resected STC patients, we demonstrated that, together with an important and significant decrease of enteric neurons (due to increased apoptotic phenomena) and ICC compared to controls, these patients also displayed a significant decrease of enteric glial cells (EGC) in both the myenteric and the submucous plexus, a decrease not due to increased apoptotic phenomena (31). Since similar neuropathological abnormalities were found in the terminal ileum of these patients, we suggested that the neuropathologic process might not be limited to the colon in these subjects (32).

In another investigation, conducted on the ENS of patients with OD (in whom the pathophysiologic mechanisms are thought to be different) undergoing surgery for refractory symptoms, we found that, compared to control, a significant reduction of the enteric neurons only in the submucosal plexus, whereas there was a loss of EGC in both the myenteric and the submucosal plexus. No differences between patients and controls were found concerning ICC and the number of apoptotic neurons (33).

Subsequently, we studied colonic specimens of patients with idiopathic megacolon and Chagas's disease, undergoing surgery for intractable constipation (often the only therapeutic option in these cases (34); in both conditions we found a decreased number of of enteric neurons and of EGC (the latter being more accentuated in chagasic patients) (35). Interestingly, other authors have then reported that, in patients with chagasic megacolon, the destruction of the enteric neurons is preceded by the loss of EGC, leading to the hypothesis that this cell population might prevent colonic dilatation, protecting the ENS against the inflammatory process and neuronal destruction (36).

Chronic constipation is a frequent feature of diverticular disease of the colon (37), but its pathophysiologic basis still remain largely unknown (38). In particular, very few data are available concerning ENS abnormalities in this condition (39). However, we and other authors documented that these patients, compared to controls, display a normal number of myenteric and submucosal plexus neurons, whereas ICC and EGC are significantly decreased (40, 41).

Unifying pathophysiologic findings: the importance of EGC

From the above considerations, based on our own and other authors' work, it may be inferred that there is a common factor that unifies several conditions characterized by constipation, factor represented by a loss of colonic EGC. This and other observations have recently spurred us and other investigators to consider this cell population as an important determinant for gastrointestinal motor activity (especially in the colon) (42-45) and a factor of paramount importance in the pathophysiology of constipation (46, 47).

How can EGC be involved in such instances?

EGC represent most of the cell population of enteric ganglia, with a ratio of 4:1 compared to neurons (48) and, in addition to have a mechanical support function due to the adherence to the surface of enteric ganglia and nerve by means of filaments of glial fibrillary acidic protein (49). Also, they display several other functions such as participation in neurotransmission (50-52) and promotion of synaptic communication in enteric neurons (53), in the maintenance of the homeostatic function of the enteric neurons (54, 55), in inflammatory processes and immune functions of the gut (56, 57), and in visceral pain (58).

How EGC participate in the pathogenesis of constipation

It must be firstly taken into account that, notwithstanding the above considerations, most data on EGC function originate from animal studies, and human data (apart from those reported above) are very scarce. However, we feel that some considerations and hypotheses may be formulated.

For instance, the absence of trophic glial factor is responsible for the loss of myenteric neurons containing substance P (an excitatory transmitter), which in turn causes decrease of intestinal transit (59), and the loss of EGC impairs motility and transit in the gut (60). Since EGC provides a feedback system for ICC to modulate slow wave activity, their decrease in constipated patients, in whom ICC are also often decreased or absent, might further impair the reduced pacemaker signals originating from these cells (61).

Thus, on the above grounds, we have hypothesized that the decrease/loss of EGC (together with other factors, such as the concomitant decrease or loss of enteric neurons, ICC, enteric neurotransmitters, variation of colonic mast cell population (46, 47, 62)) plays a pivotal role in the pathogenesis of constipation. A decrease/loss of EGC, through impairment of neurotrophic factors, might for instance be responsible (similarly to that documented in experimental animal models) for degeneration of the enteric neurons population. In this respect, it is worth noting that in patients with "idiopathic" constipation in addition to the loss of EGC is often documented the concomitant decrease of enteric neurons due increased apoptotic phenomena (31, 32, 63); on the other hand, in constipated patients with degenerative conditions of the central nervous system (for instance, Alzheimer's disease) no EGC loss has been reported, and the reduction of enteric neurons is not due to apoptotic phenomena (64).

How can a selective loss/decrease of EGC be explained? Interestingly, recent data suggest that an infectious agent might play a role, as shown by the localization and multiplication of *Mycobacterium avium* subspecies and by the expression of prion protein in these cells (65-67). Moreover, a role for intestinal flora in the plasticity of the ENS has been recently hypothesized, since the population of EGC may be modulated by altered luminal environment (68).

The decrease of EGC could also be due to an aging process (69, 70), even though such data in human beings are only available for enteric

neurons (71). Other damaging factors on the ENS, such as that hypothesized by the use of anthraquinone laxatives, have not been confirmed with modern immunohistochemical techniques (72). On the other hand, the demonstration of chromosomal abnormalities of enteric neurons and EGC in severely constipated patients requiring surgery suggests the presence of a genetic background possibly responsible for the loss of these elements (73).

Concluding remarks

Perhaps it is time that EGC are viewed not simply as the glue of the gut, but as important and pivotal cells that synchronize the various elements of the ENS. With this respect, the demonstration that several entities characterized by constipation display a decrease or loss of EGC, should led (of course, in addition to other abnormalities) to classify constipation not as a "functional" or "idiopathic" condition, but as a neuro-gliopathy of the gut (46, 47, 74). Further studies are needed to establish a more precise role for EGC in the pathophysiology of gut motility.

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